UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,884	07/22/2003	Richard Harkins	51791AUSC1	1667

27586 7590 06/05/2006

BERLEX BIOSCIENCES
PATENT DEPARTMENT
2600 HILLTOP DRIVE
P.O. BOX 4099
RICHMOND, CA 94804-0099

EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/624,884	HARKINS ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/22/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Election/Restrictions

1. Applicant's election of the invention of Group I, claims 1-25 in the reply filed on 19 May 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 26-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1-25 are under examination.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 22 July 2003 has been fully considered and an examiner-initialed copy of the IDS is attached to this Office Action.

Specification

5. The disclosure is objected to because of the following informalities:

a. The brief description of the drawings for Figure 9 discloses V_H_2m (SEQ ID NO:28), however, Figure 9 discloses B_3M, V_H. Similarly, the brief description of the drawings for Figure 10 discloses V_H_3m (SEQ ID NO:31), however, Figure 10 discloses C_2m, V_H. Clarification and/or correction are requested.

b. The claim for priority on the first line of the specification needs to be updated with the U.S. Patent number for USSN 09/732,357, which is U.S. Patent 6,682,902.

c. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. For example, see page 39, line 37. Applicant's cooperation is requested in reviewing and correction any additional embedded hyperlinks and/or other form of browser-executable code of which applicant may become aware in the specification. See MPEP § 608.01.

d. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention, i.e., human antibodies to the RG1 polypeptide.

e. The use of the trademarks Phagescript®, Bluescript® Xenomouse™ and LifeSeq® has been noted in this application (e.g., see pg. 26, line 13, pg. 28, line 11, pg. 34, line 14, pg. 47, line 3). It should be capitalized wherever it appears and be accompanied by the generic terminology. Applicant's cooperation is requested in reviewing and correcting any additional trademarks of which applicant may become aware of in the specification.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Objections

6. Claims 20-21 and 23-24 are objected to because of the following informalities:

Claims 20-21 and 23-24 are objected to in the recitation "selected from a group consisting of...", which is not a proper Markush group. Consider revising with "selected from the group consisting of...". See MPEP 2173.05(h).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claim 1 and 3-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1 and 3-25 are vague and indefinite in the recitation of "an RG1 polypeptide" as the sole means of identifying the antibody specificity referred to in the claims. The use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. Amending the claims to specifically and uniquely identify the RG1 polypeptide, for example, by SEQ ID number can obviate this rejection.

b. Claim 20 contains the trademark/trade name Taxol™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second

paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a cytotoxic agent and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1 and 3-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.

> 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the

courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to isolated human antibodies and antigen-binding fragments thereof as well as immunoconjugates thereof wherein the human antibodies specifically bind to an epitope present in "an RG1 polypeptide". Thus, the instant invention encompasses employing any human antibody that binds any "RG1 polypeptide", yet the instant specification does not provide sufficient written description as to the structural features of any "RG1 polypeptide" and the correlation between the chemical structure and the function of the genus of "RG1 polypeptides. The specification defines "RG1" as referring to the polypeptide having the amino acid sequence of SEQ ID NO:2, variants and derivatives thereof, and fragments of SEQ ID NO:2, variants and derivatives thereof, wherein "variants", "fragments" and "derivatives" mean a polypeptide which retains essentially the same biologic and/or immunologic activity as the polypeptide of SEQ ID NO:2 (see pg. 4, lines 35-39). Further, the specification discloses that "derivative" refers to polypeptides derived from naturally occurring *rg1*, RG1, or from antibodies binding RG1, by chemical modifications, amino acid insertions and substitutions (see pg. 7). The specification discloses that the claimed "RG1 polypeptide" encompass proteins which are at least 80%, 85%, 90%, 95% or 99% identical to the original sequence (i.e., SEQ ID NO:2) (see pp. 8). Thus, there is substantial variance within the genus of RG1 polypeptides.

The specification does not provide sufficient written description as to the structural features of the claimed genus of RG1 polypeptides and the correlation between the chemical structure and function of the genus, such as structural domains or motifs that are essential and distinguish members of the genus from those excluded. The instant specification does not disclose nor identify "an RG1 polypeptide" other than the RG1 polypeptide of SEQ ID NO:2. MPEP 2163 II.A.3(a) states "disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties or deposit in a public depository provides adequate written description of an antibody claimed by its binding affinity to that antigen" (citing Noelle v. Lederman, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004))

A "representative number of species" means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]. "See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004) "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus

by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).

For example, Lederman et al (Molecular Immunology 28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document).

For example, Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other activities when constructing analogs (see entire document).

With respect to naturally occurring *rg1*, RG1 or from antibodies binding RG1, the general knowledge in the art concerning variants does not provide any indication of how the structure of one variant is representative of unknown variants. Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome... and differing from other alleles of that locus at one or more mutational sites (pg. 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of the RG1 polypeptide of SEQ ID NO:2 the skilled artisan cannot envision the detailed structure of the encompassed RG1 polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the

method of isolation. Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

The instant claims do not provide sufficient structural and function characteristics coupled with a known or disclosed correlation between function and structure. Sine the disclosure does not describe the common attributes or characteristics that identify members of the genus of RG1 polypeptides, including naturally occurring derivatives, fragments and variants of the RG1 polypeptide of SEQ ID NO:2. Applicant's reliance on the RG1 polypeptide of SEQ ID NO:2 disclosed in the specification as-filed does not provide sufficient written description for the genus of "RG1 polypeptides" encompassed by the claimed immunologic activity in view of the above evidence, which indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement

that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddles v.Baird*, 30 USPQ2d 1481, 1483. In *Fiddles v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad genus. Claims 1 and 3-25 are broadly generic to all possible RG1 polypeptides encompassed by the claims. The possible variations are enormous to any class of polypeptide. Since the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. Here, though the claims may recite some functional characteristics (i.e., immunologic activity), the claims lack written description because there is no disclosure of a correlation between function and structure of "*an RG1 polypeptide*" beyond that disclosed in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of "an RG1 polypeptide" that does not comprise the amino acid sequence of SEQ ID NO:2.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the entire scope of the claimed invention.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

11. Claims 1, 3-8 and 17-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) an isolated human antibody and antigen-binding fragments thereof that specifically binds RG1 and conjugates of said human antibodies and (ii) an isolated human antibody and antigen-binding fragments thereof comprising a light chain variable region comprising the amino acid sequence of SEQ ID NO:26 or SEQ ID NO:29 or comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:27, 28, 30 or 31, wherein the human antibody or antigen-binding fragments thereof specifically bind RG1, does not reasonably provide enablement for isolated human antibody *variants* and antigen-

binding fragments thereof and an isolated human antibody and antigen-binding fragments thereof comprising a light chain variable region comprising an amino acid sequence having at least 80% sequence identity with SEQ ID NO:26 or SEQ ID NO:29 or comprising a heavy chain variable region comprising an amino acid sequence having at least 80% sequence identity with SEQ ID NO:27, 28, 30 or 31. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is engineered antibodies and cancer immunotherapy where the relative level of skill of those in the art is deemed to be high.

The claims are broadly drawn to variants of an isolated human antibody and antigen-binding fragments thereof that bind to an epitope present in an RG1 polypeptide and having a K_D equal to or less than 1μM or 10nM and conjugates of said human antibody variants, as well as an isolated human antibody and antigen-binding fragments thereof comprising a light chain variable region having at least 80% amino acid

sequence identity with SEQ ID NO:26 or 29 or comprising a heavy chain variable region having at least 80% amino acid sequence identity with SEQ ID NO:27, 28, 30 or 31. Thus, the claims broadly encompass human antibodies comprising a modified variable region or regions comprising amino acid insertions, deletions and/or substitutions, which broadly embraces human antibodies that do not contain a full set of 6 CDRs from the heavy chain variable (VH) domain and the light chain variable (VL) domain and do not bind RG1. For example, for a typical variable region of about 110 amino acids in length, the claim language encompasses up to 22 (i.e., 80% sequence identity) amino acid insertions, deletions and/or substitutions and hence, broadly embraces deletion of a CDR.

The specification discloses only antibodies that specifically bind RG1 and comprise all 6 CDRs, three from the VH domain and three from the VL domain (see Examples 4-12). The specification does teach human antibody variants that specifically bind RG1 or human antibodies that do not contain all six CDRs, three from the VH domain and three from the VL domain that bind RG1 or human antibodies comprising a light chain variable region having at least 80% amino acid sequence identity with SEQ ID NO:26 or 29 or comprising a heavy chain variable region having at least 80% amino acid sequence identity with SEQ ID NO:27, 28, 30 or 31, wherein the human antibodies bind RG1. There are no working examples of human antibody variants that bind RG1.

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which

consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79:1979-1983, March 1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Coleman (Research in Immunology, 145:33-36, 1994) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column). It is unlikely that human antibodies comprising a variable region which does not contain all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their correct spatial orientation have the requisite RG1

binding function. For example, Hanson et al (U.S. Patent 6,682,736) teach a human monoclonal antibody comprising a light chain variable region that is 93% identical to the instantly claimed light chain variable region of SEQ ID NO:26 and the human antibody binds CTLA-4 (see the alignment attached to the back of this Office Action; Exhibit C). The specification provides insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing human antibodies comprising a light chain variable region having at least 80% sequence identity with SEQ ID NO:26 or 29 or comprising a heavy chain variable region having at least 80% sequence identity with SEQ ID NO:27, 28, 30 or 31 and less than all six CDRs that bind RG1. Although the specification at page 15 discloses that antibody variants can be made using any techniques and guideline for conservative and non-conservative mutations, and variants include substitution, deletion or insertion and particularly, substituting one or mare hypervariable region (i.e., CDR) residues, the specification does not provide sufficient guidance or direction as to the general tolerance to modification and extent of such tolerance in the variable regions; the specific positions of the variable regions which can be predictably modified and which regions are critical for maintaining specificity and affinity for RG1. The specification provides no direction or guidance regarding how to produce the myriad of human antibodies, which contain a modified variable region as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. The scope of the claims must bear a reasonable correlation with the scope of enablement. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul W. E., Rudikoff et al, Coleman P. M. and Hanson et al, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed human antibody variants that bind RG1 with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed human antibody variants and absent working examples providing evidence which is reasonably predictive that the claimed human antibody variants bind RG1, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 1-2 and 15-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Hastings et al (U.S. Patent 5,871,969, field 2/12/1997, cited on Ids filed 7/22/03).

The claims are drawn to an isolated human antibody or antigen-binding fragment thereof that specifically binds to an epitope present in an RG1 polypeptide which has that amino acid sequence of SEQ ID NO:2, wherein the antigen-binding fragment is a

Fv, F(ab'), F(ab')2 or scFv. Further, the claims are drawn an antibody which binds the same epitope as the epitope bound by the human antibody comprising the light chain variable region of SEQ ID NO:26 and a heavy chain variable region selected from SEQ ID NO:27 or 28 or the human antibody comprising the light chain variable region of SEQ ID NO:29 and a heavy chain variable region selected from SEQ ID NO:30 or 31.

Hastings teach human antibodies and antigen-binding fragments thereof including Fab fragments and single-chain antibodies (i.e., scFv) that specifically bind the a polypeptide comprising the amino acid sequence of SEQ ID NO:2, which is 99% identical to the claimed RG1 polypeptide of SEQ ID NO:2 (see Exhibit A attached to the back of this office action) (see entire document, particularly columns 25-26 and Fig. 1). Therefore, it appears that Hastings et al have produced human antibodies that would necessarily bind the same epitope that the claimed human antibodies bind. Given the substantial structural identity of the polypeptide of the prior art and the claimed polypeptide of SEQ ID NO:2 (i.e., 99% sequence identity), one of ordinary skill in the art would reasonably conclude that Hastings et al's human antibodies also possesses the same structural and functional properties as those of the human antibodies claimed and, therefore, it appears that Hastings et al have produced human antibodies that are identical to the claimed human antibodies. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed human antibodies with the human antibodies of Hastings et al, the burden of proof is upon Applicant to show a distinction between the structural and functional characteristics of the claimed human antibodies and the human antibodies of the prior art. See In re Best, 562 F.2d 1252,

195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). See MPEP 2112.01.

Thus, Hastings et al anticipate the claims.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-4 and 15-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ali et al (US 2005/0147556 A1, priority to 10/19/1998) in view of Kucherlapati et al (U.S. Patent 6,150,584, filed 10/2/1996) and Devaux et al (U.S. Patent 6,824,780 B1, 10/29/1999).

The claims are drawn to an isolated human antibody or antigen-binding fragment thereof that specifically binds to an epitope present in an RG1 polypeptide which has that amino acid sequence of SEQ ID NO:2, wherein binding occurs with a K_D equal to or less than 1μM or 10nM and wherein the antigen-binding fragment is a Fv, F(ab'), F(ab')2, scFv, minibody or diabody and wherein said human antibody or antigen-binding fragment thereof is conjugated (i.e., immunconjugate) to a therapeutic agent or a detectable marker, wherein the therapeutic agent is a cytotoxic agent including radioisotopes and the detectable marker is a radiolabel, an enzyme, a chromophore, or a fluorescer and wherein the therapeutic agent or detectable marker is conjugated via the chelator MX-DTPA. Further, the claims are drawn an antibody which binds the same epitope as the epitope bound by the human antibody comprising the light chain variable region of SEQ ID NO:26 and a heavy chain variable region selected from SEQ ID NO:27 or 28 or the human antibody comprising the light chain variable region of SEQ ID NO:29 and a heavy chain variable region selected from SEQ ID NO:30 or 31.

Ali et al teach antibodies that specifically bind to a prostate cancer polypeptide (i.e., SEQ ID NO:2) that is 99% identical to the claimed RG1 polypeptide of SEQ ID

NO:2 (see Exhibit B attached to the back of this office action), as well as immunoconjugates comprising the antibody conjugated to a radioisotope (^{67}Cu, ^{186}Re, ^{111}In or ^{99m}Tc), paramagnetic metal, or a cytotoxic agent including an enzyme, toxin, drug or prodrug for diagnosis and treatment in prostate cancer patients (see entire document, particularly pages 2 and 4 and SEQ ID NO:2). Ali et al do not specifically teach an human antibodies or antigen-binding fragments thereof having a K_D less than 1μM or 10nM, wherein the antibody fragment is a Fv, F(ab'), F(ab')2 or wherein the therapeutic agent or detectable marker is conjugated using the chelator MX-DTPA. These deficiencies are made up for in the teachings of Kucherlapati et al and Devaux et al.

Kucherlapati et al teach human antibodies having a K_D less than 1μM or 10nM, and human antibodies are less immunogenic than in human patients compared to nonhuman antibodies and better suited for human immunotherapy (see entire document, particularly column 6, lines 35-47 and column 9).

Devaux et al teach human antibodies and antigen-binding fragments thereof including Fab, Fab', F(ab')2 and scFv fragments and conjugates comprising a cytotoxic or detectable radiolabel wherein MX-DTPA is an exemplary chelating agent for radionuclide conjugation for prostate cancer therapy (see entire document, particularly columns 8-9, 24-25 and 34-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced prostate specific (i.e., SEQ ID NO:2 of Ali et al) human antibody and antigen-binding fragments thereof including Fab,

Fab', F(ab')2 and scFv fragments having a K_D less than 1μM or 10nM and conjugated to a cytotoxic agent or detectable label via MX-DTPA for therapeutic benefit in human prostate cancer patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced prostate specific (i.e., SEQ ID NO:2 of Ali et al) human antibody and antigen-binding fragments thereof including Fab, Fab', F(ab')2 and scFv fragments having a K_D less than 1μM or 10nM and conjugated to a cytotoxic agent or detectable label via MX-DTPA for therapeutic benefit in human prostate cancer patients in view of Ali et al and Kucherlapati et al and Devaux et al because Ali et al teach antibodies that specifically bind to a prostate cancer polypeptide (i.e., SEQ ID NO:2) that is 99% identical to the claimed RG1 polypeptide of SEQ ID NO:2 (see Exhibit B attached to the back of this office action), as well as immunoconjugates comprising the antibody conjugated to a radioisotope (^{67}Cu, ^{186}Re, ^{111}In or ^{99m}Tc), paramagnetic metal, or a cytotoxic agent including an enzyme, toxin, drug or prodrug for diagnosis and treatment in prostate cancer patients and Kucherlapati et al teach human antibodies having a K_D less than 1μM or 10nM, and human antibodies are less immunogenic in human patients compared to non-human antibodies and better suited for human therapy and Devaux et al teach human antibodies and antigen-binding fragments thereof including Fab, Fab', F(ab')2 and scFv fragments and conjugates thereof comprising a cytotoxic or detectable radiolabel wherein MX-DTPA is an exemplary chelating agent for radionuclide conjugation for prostate cancer immunotherapy. Therefore, one of ordinary skill in the

art at the time the invention was made would have been motivated to produce high affinity human antibodies and antigen-binding fragments thereof including Fab, Fab', F(ab')2 and scFv fragments having a K_D less than 1μM or 10nM and conjugated to a cytotoxic agent or detectable label via MX-DTPA for therapeutic benefit in human prostate cancer patients, since human antibodies are less immunogenic in human patients compared to non-human antibodies and better suited for human therapy. Thus, there would be an advantage to using human antibodies and human antibody immunoconjugates for the delivery of a therapeutic or diagnostic agent in human prostate cancer patients and given the substantial structural identity of the polypeptide of the prior art and the claimed polypeptide of SEQ ID NO:2 (i.e., 99% sequence identity), one of ordinary skill in the art would reasonably conclude that the human antibodies of Ali et al and Kucherlapati et al and Devaux et al also possesses the same structural and functional properties as those of the human antibodies claimed and, therefore, it appears that Ali et al and Kucherlapati et al and Devaux et al have produced human antibodies that are identical to the claimed human antibodies. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed human antibodies with the human antibodies of Ali et al and Kucherlapati et al and Devaux et al, the burden of proof is upon Applicant to show an unobvious between the structural and functional characteristics of the claimed human antibodies and the human antibodies of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). See MPEP 2112.01.

Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced prostate specific (i.e., SEQ ID NO:2 of Ali et al) human antibody and antigen-binding fragments thereof including Fab, Fab', F(ab')2 and scFv fragments having a K_D less than 1μM or 10nM and conjugated to a cytotoxic agent or detectable label via MX-DTPA for therapeutic benefit in human prostate cancer patients in view of Ali et al and Kucherlapati et al and Devaux et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

16. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

17. Claims 1-16 and 18-25 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-16 and 18-25 of copending Application No. 10/895,183. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claim 17 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 17 of copending Application No. 10/895,183.

Claim 17 is drawn to isolated RG1 specific human Fv, F(ab'), F(ab')2, and scFv fragments.

Claim 17 of copending Application No. 10/895,183 is also drawn to isolated RG1 specific human Fv, F(ab'), F(ab')2, scFv, minibody and diabodies.

Thus, claim 17 of the present application is an obvious variant of claim 17 of copending Application No. 10/895,183 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an isolated RG1 specific human Fv, F(ab'), F(ab')2 or scFv for therapeutic

benefit in human prostate cancer patients in view of claim 17 of copending Application No. 10/895,183.

This is a provisional obviousness-type double patenting rejection.

20. Claims 1-4 and 15-25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-9 of U.S. Patent No. 6,682,902 B2 in view of Kucherlapati et al (U.S. Patent 6,150,584, 10/2/1996) and Devaux et al (U.S. Patent 6,824,780 B1, 10/29/1999). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims have been described supra.

Claims 4-9 of U.S. Patent No. 6,682,902 B2 are drawn to polyclonal and monoclonal antibodies and antibody fragments that specifically bind to one or more epitopes present in a human RG1 polypeptide having the amino acid sequence of SEQ ID NO:2, wherein the antibody specifically binds to the amino acid sequence of SEQ ID NO:8, 10, 11 or 12, which are the same RG1 peptides used to raise the antibodies claimed in the instant application and thus, necessarily present in the polypeptide of SEQ ID NO:2. The claims in U.S. Patent 6,682,902 B2 do not recite a human antibody that specifically binds to an epitope present in an RG1 polypeptide having the amino acid sequence of SEQ ID NO:2 wherein the binding occurs with a K_D less than 1μM or 10nM or wherein the antibody fragments are an Fv, F(ab'), F(ab')2, scFv or diabody and wherein the human antibody or fragment thereof is conjugated to a therapeutic agent that is a cytotoxic agent or a detectable marker that is a radiolabel, an enzyme, a

chromophore or a fluorescer and wherein conjugation is via the chelating agent MX-DTPA. These deficiencies are made up for in the teachings of Kucherlapati et al and Devaux et al.

Kucherlapati et al have been described supra.

Devaux et al have been described supra.

Claims 1-4 and 15-25 of the present application are obvious variants of claims 4-9 of U.S. Patent 6,682,902 B2 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced human antibodies and Fv, F(ab'), F(ab')2 and scFv fragments thereof that specifically bind to the RG1 epitopes of SEQ ID NO:8, 10, 11 and 12 (necessarily present in the RG1 polypeptide of SEQ ID NO:2), wherein the human antibodies have a K_D less than 1μM or 10nM and are conjugated to a cytotoxic agent or detectable marker as recited in the instant claims or conjugated to a cytotoxic or detectable radiolabel via MX-DTPA for therapeutic benefit in human prostate cancer patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced human antibodies and Fv, F(ab'), F(ab')2 and scFv fragments thereof that specifically bind to the RG1 epitopes of SEQ ID NO:8, 10, 11 and 12 (necessarily present in the RG1 polypeptide of SEQ ID NO:2), wherein the human antibodies have a K_D less than 1μM or 10nM and are conjugated to a cytotoxic agent or detectable marker as recited in the instant claims or conjugated to a cytotoxic or detectable radiolabel via MX-DTPA for therapeutic benefit in human prostate cancer patients in view of Kucherlapati et al and Devaux et al because

Kucherlapati et al teach human antibodies having a K_D less than 1μM or 10nM, and human antibodies are less immunogenic than in human patients compared to nonhuman antibodies and better suited for human therapy and Devaux et al teach human antibodies and antigen-binding fragments thereof including Fv, F(ab'), F(ab')2, scFv and conjugates thereof comprising a cytotoxic or detectable radiolabel wherein MX-DTPA is an exemplary chelating agent for radionuclide conjugation for prostate cancer immunotherapy. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce high affinity human antibodies and antigen-binding fragments thereof including Fv, F(ab'), F(ab')2 and scFv specific for the RG1 epitopes of SEQ ID Nos:8, 10, 11 and 12 and having a K_D less than 1μM or 10nM and conjugated to various cytotoxic agents or detectable markers including a cytotoxic or detectable radiolabel conjugated via MX-DTPA, which is an ideal chelating agent for conjugation of a radionuclide to an antibody according to Devaux et al. Thus, there would be an advantage to using high affinity human antibody conjugates for human prostate cancer therapy as human antibodies are less immunogenic in human patients compared to non-human antibodies. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced human antibodies and Fv, F(ab'), F(ab')2 and scFv fragments thereof that specifically bind to the RG1 epitopes of SEQ ID NO:8, 10, 11 and 12 (necessarily present in the RG1 polypeptide of SEQ ID NO:2), wherein the human antibodies have a K_D less than 1μM or 10nM and are conjugated to a cytotoxic agent or detectable marker as recited in the instant claims or conjugated to a cytotoxic or

detectable radiolabel via MX-DTPA for therapeutic benefit in human prostate cancer patients in view of claims 4-9 of U.S. Patent 6,682,902 B2 and Kucherlapati et al and Devaux et al.

Claims 1-4 and 15-25 are directed to an invention not patentably distinct from claims 4-9 of commonly assigned U.S. Patent 6,682,902 B2. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent 6,682,902 B2 discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

21. Claims 1-4 and 15-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 24-29, 31-34 and

44 of copending Application No. 10/616,279 in view of Kucherlapati et al (U.S. Patent 6,150,584, 10/2/1996) and Devaux et al (U.S. Patent 6,824,780 B1, 10/29/1999). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims have been described supra.

Claims 24-29, 31-34 and 44 of copending Application No. 10/616,279 are drawn to isolated antibodies and antibody fragments that specifically bind to a polypeptide comprising the amino acid sequence of SEQ ID NO:2, wherein the antibody specifically binds to the amino acid sequence of SEQ ID NO:8, 10, 11 or 12, which are the same RG1 peptides used to raise the antibodies claimed in the instant application and thus, necessarily present in the RG1 polypeptide of SEQ ID NO:2 and wherein the antibodies are polyclonal, monoclonal, chimeric, humanized and human antibodies, and conjugates of said antibodies (i.e., immunoconjugates) as well as Fv, F(ab'), F(ab')2 fragments comprising a therapeutic agent that is a cytotoxic agent. Claims 24-29, 31-34 and 44 of copending Application No. 10/616,279 do not recite a human antibody and fragments thereof that specifically bind to the RG1 epitopes of SEQ ID NO:8, 10, 11 and 12 wherein the binding occurs with a K_D less than 1μM or 10nM or wherein the antibody fragments are an Fv, F(ab'), F(ab')2, scFv or wherein the human antibody is conjugated to a cytotoxic or detectable radiolabel conjugated using MX-DTPA. These deficiencies are made up for in the teachings of Kucherlapati et al and Devaux et al.

Kucherlapati et al have been described supra.

Devaux et al have been described supra.

Claims 1-4 and 15-25 of the present application are obvious variants of claims 24-29, 31-34 and 44 of copending Application No. 10/616,279 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced human antibodies and Fv, F(ab'), F(ab')2, and scFv fragments thereof that specifically bind to the RG1 epitopes of SEQ ID NO:8, 10, 11 and 12 (necessarily present in the RG1 polypeptide of SEQ ID NO:2), wherein the human antibodies have a K_D less than 1μM or 10nM and are conjugated to a cytotoxic agent or detectable marker as recited in the instant claims or conjugated to a cytotoxic or detectable radiolabel via MX-DTPA for therapeutic benefit in human prostate cancer patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced human antibodies and Fv, F(ab'), F(ab')2, and scFv fragments thereof that specifically bind to the RG1 epitopes of SEQ ID NO:8, 10, 11 and 12 (necessarily present in the RG1 polypeptide of SEQ ID NO:2), wherein the human antibodies have a K_D less than 1μM or 10nM and are conjugated to a cytotoxic agent or detectable marker as recited in the instant claims or conjugated to a cytotoxic or detectable radiolabel via MX-DTPA for therapeutic benefit in human prostate cancer patients in view of 24-29, 31-34 and 44 of copending Application No. 10/616,279 and Kucherlapati et al and Devaux et al because Kucherlapati et al teach human antibodies having a K_D less than 1μM or 10nM, and human antibodies are less immunogenic than in human patients compared to nonhuman antibodies and better suited for human therapy and Devaux et al teach human antibodies and antigen-binding

fragments thereof including Fv, F(ab'), F(ab')2, scFv and diabodies and conjugates thereof comprising a cytotoxic or detectable radiolabel wherein MX-DTPA is an exemplary chelating agent for radionuclide conjugation for prostate cancer immunotherapy. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce high affinity human antibodies and antigen-binding fragments thereof including Fv, F(ab'), F(ab')2, scFv and diabodies specific for the RG1 epitopes of SEQ ID Nos:8, 10, 11 and 12 and having a K_D less than 1μM or 10nM and conjugated to various cytotoxic agents or detectable markers including a radiolabel conjugated via MX-DTPA, which is an ideal chelating agent for conjugation of a radionuclide to an antibody according to Devaux et al. Thus, there would be an advantage to using high affinity human antibody conjugates for human prostate cancer therapy as human antibodies are less immunogenic in human patients compared to nonhuman antibodies. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced human antibodies and Fv, F(ab'), F(ab')2, and scFv fragments thereof that specifically bind to the RG1 epitopes of SEQ ID NO:8, 10, 11 and 12 (necessarily present in the RG1 polypeptide of SEQ ID NO:2), wherein the human antibodies have a K_D less than 1μM or 10nM and are conjugated to a cytotoxic agent or detectable marker as recited in the instant claims or conjugated to a cytotoxic or detectable radiolabel via MX-DTPA for therapeutic benefit in human prostate cancer patients in view of 24-29, 31-34 and 44 of copending Application No. 10/616,279 and Kucherlapati et al and Devaux et al.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

SHEELA HUFF
PRIMARY EXAMINER

Exhibit A

```
RESULT 7
US-08-799-173A-2
; Sequence 2, Application US/08799173A
; Patent No. 5871969
; GENERAL INFORMATION:
;   APPLICANT:  HASTINGS, GREGG,
;   APPLICANT:  PATRICK J. DILLON
;   TITLE OF INVENTION:  HUMAN NEURONAL ATTACHMENT FACTOR-1
;   NUMBER OF SEQUENCES:  18
;   CORRESPONDENCE ADDRESS:
;     ADDRESSEE:  HUMAN GENOME SCIENCES,INC.
;     STREET:  9410 KEY WEST AVENUE
;     CITY:  ROCKVILLE
;     STATE:  MD
;     COUNTRY:  USA
;     ZIP:  20850
;   COMPUTER READABLE FORM:
;     MEDIUM TYPE:  Floppy disk
;     COMPUTER:  IBM PC compatible
;     OPERATING SYSTEM:  PC-DOS/MS-DOS
;     SOFTWARE:  PatentIn Release #1.0, Version #1.30
;   CURRENT APPLICATION DATA:
;     APPLICATION NUMBER:  US/08/799,173A
;     FILING DATE:  11-FEB-1997
;     CLASSIFICATION:  536
;   ATTORNEY/AGENT INFORMATION:
;     NAME:  BROOKES, ANDERS A.
;     REGISTRATION NUMBER:  36,373
;     REFERENCE/DOCKET NUMBER:  PF226
;   TELECOMMUNICATION INFORMATION:
;     TELEPHONE:  (301) 309-8504
;     TELEFAX:  (301) 309-8512
; INFORMATION FOR SEQ ID NO:  2:
;   SEQUENCE CHARACTERISTICS:
;     LENGTH:  331 amino acids
;     TYPE:  amino acid
;     TOPOLOGY:  linear
;   MOLECULE TYPE:  protein
US-08-799-173A-2

  Query Match             99.0%;  Score 1742;  DB 1;  Length 331;
  Best Local Similarity   99.4%;  Pred. No. 7.4e-164;
  Matches  329;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          1 MENPSPAAALGKALCALLLATLGAAGQPLGGESICSAGAPAKYSITPTGKWSQTAFPKQY 60
              ||||||||||||||||||||||||||||||||||| | ||||||||||||||||||||
Db          1 MENPSPAAALGKALCALLLATLGAAGQPLGGESICSARALAKYSITPTGKWSQTAFPKQY 60

Qy         61 PLFRPPAQWSSLLGAAHSSDYSMWRKNQYVSNGLRDFAERGEAWALMKEIEAAGEALQSV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 PLFRPPAQWSSLLGAAHSSDYSMWRKNQYVSNGLRDFAERGEAWALMKEIEAAGEALQSV 120

Qy        121 HAVPSAPAVPSGTGQTSAELEVQRRHSLVSFVVRIVPSPDWFVGVDSLDLCDGDRWREQA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 HAVPSAPAVPSGTGQTSAELEVQRRHSLVSFVVRIVPSPDWFVGVDSLDLCDGDRWREQA 180

Qy        181 ALDLYPYDAGTDSGPTPSSPNFATIPQDTVTEITSSSPSHPANSFYYPRLKALPPIARVT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 ALDLYPYDAGTDSGPTPSSPNFATIPQDTVTEITSSSPSHPANSFYYPRLKALPPIARVT 240

Qy        241 LVRLRQSPRAFIPPAPVLPSRDNEIVDSASVPETPLDCEVSLWSSWGLCGGHCGRLGTKS 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 LVRLRQSPRAFIPPAPVLPSRDNEIVDSASVPETPLDCEVSLWSSWGLCGGHCGRLGTKS 300

Qy        301 RTRYVRVQPANNGSPCPELEEEAECVPDNCV 331
              |||||||||||||||||||||||||||||||
Db        301 RTRYVRVQPANNGSPCPELEEEAECVPDNCV 331
```

Exhibit B

```
RESULT 13
US-10-929-973-2
; Sequence 2, Application US/10929973
; Publication No. US20050147556A1
; GENERAL INFORMATION:
;  APPLICANT: Ali, Shijath M.
;  APPLICANT:  Sun, Yongming
;  APPLICANT:  Salceda, Susana
;  APPLICANT:  Recipon, Herve
;  APPLICANT:  Cafferkey, Robert
;  APPLICANT:  DIADEXUS LLC
;  TITLE OF INVENTION: A Novel Method of Diagnosing, Monitoring, Staging,
;  TITLE OF INVENTION:  Imaging and Treating Prostate Cancer
;  FILE REFERENCE: DEX-0048
;  CURRENT APPLICATION NUMBER: US/10/929,973
;  CURRENT FILING DATE:  2004-08-30
;  PRIOR APPLICATION NUMBER: US/09/807,200
;  PRIOR FILING DATE: 2001-05-29
;  PRIOR APPLICATION NUMBER: 60/104,741
;  PRIOR FILING DATE: 1998-10-19
;  NUMBER OF SEQ ID NOS: 4
;  SOFTWARE: PatentIn Ver. 2.0
; SEQ ID NO 2
;   LENGTH: 331
;   TYPE: PRT
;   ORGANISM: Homo sapiens
US-10-929-973-2

  Query Match            99.3%;  Score 1747;  DB 5;  Length 331;
  Best Local Similarity  99.4%;  Pred. No. 2.4e-149;
  Matches  329;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          1 MENPSPAAALGKALCALLLATLGAAGQPLGGESICSAGAPAKYSITPTGKWSQTAPPKQY 60
              ||||||||||||||||||||||||||||||||||| |||||||||||||||||||||||
Db          1 MENPSPAAALGKALCALLLATLGAAGQPLGGESICSARAPAKYSITPTGKWSQTAPPKQY 60

Qy         61 PLPRPPAQWSSLLGAAHSSDYSMWRKNQYVSNGLRDFAERGEAWALMKEIEAAGEALQSV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 PLPRPPAQWSSLLGAAHSSDYSMWRKNQYVSNGLRDFAERGEAWALMKEIEAAGEALQSV 120

Qy        121 HAVPSAPAVPSGTGQTSAELEVQRRHSLVSFVVRIVPSPDWFVGVDSLDLCDGDRWREQA 180
              | ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 HEVPSAPAVPSGTGQTSAELEVQRRHSLVSFVVRIVPSPDWFVGVDSLDLCDGDRWREQA 180

Qy        181 ALDLYPYDAGTDSGFTFSSPNFATIPQDTVTEITSSSPSHPANSFYYPRLKALPPIARVT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 ALDLYPYDAGTDSGFTFSSPNFATIPQDTVTEITSSSPSHPANSFYYPRLKALPPIARVT 240

Qy        241 LVRLRQSPRAFIPPAPVLPSRDNEIVDSASVPETPLDCEVSLWSSWGLCGGHCGRLGTKS 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 LVRLRQSPRAFIPPAPVLPSRDNEIVDSASVPETPLDCEVSLWSSWGLCGGHCGRLGTKS 300

Qy        301 RTRYVRVQPANNGSPCPELEEEAECVPDNCV 331
              |||||||||||||||||||||||||||||||
Db        301 RTRYVRVQPANNGSPCPELEEEAECVPDNCV 331


RESULT 14
US-10-919-215-1
; Sequence 1, Application US/10919215
```

Exhibit C

RESULT 1
US-09-472-087-14
; Sequence 14, Application US/09472087
; Patent No. 6682736
; GENERAL INFORMATION:
; APPLICANT: HANSON, DOUGLAS C.
; APPLICANT: NEVEU, MARK J.
; APPLICANT: MUELLER, EILLEN B.
; APPLICANT: HANKE, JEFFREY H.
; APPLICANT: GILMAN, STEVEN C.
; APPLICANT: DAVIS, C. GEOFFREY
; APPLICANT: CORVALAN, JOSE R.
; TITLE OF INVENTION: HUMAN MONOCLONAL ANTIBODIES TO CTLA-4
; FILE REFERENCE: ABX-PP1
; CURRENT APPLICATION NUMBER: US/09/472,087
; CURRENT FILING DATE: 1999-12-23
; PRIOR APPLICATION NUMBER: 60/113,647
; PRIOR FILING DATE: 1998-12-23
; NUMBER OF SEQ ID NOS: 147
; SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 14
; LENGTH: 235
; TYPE: PRT
; ORGANISM: Homo sapiens
US-09-472-087-14

Query Match 93.9%; Score 612.5; DB 2; Length 235;
Best Local Similarity 93.8%; Pred. No. 2.7e-50;
Matches 120; Conservative 4; Mismatches 3; Indels 1; Gaps 1;

```
Qy          1 MSTPAQLLPLLLLWLPDTTGEIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQK 60
              ||||||||||||||||||||||||||||||||||||||||||||:|||:||||||:
Db          1 MSTPAQLLPLLLLWLPDTTGEIVLTQSPGTLSLSPGERATLSCRASQSISSSFLAWYQQR 60

Qy         61 PGQAPRLLIYGASSRATGIPDRFSGSGSGSGTDFTLTISRLEPEDFAVYYCQQYSSS-LTPG 119
              |||||||||||||||||||||||||||||||||||||||||||||||||||| :|  |||
Db         61 PGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGTSPWTPG 120

Qy        120 GGTKVEIK 127
              ||||||||
Db        121 QGTKVEIK 128
```